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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/792,346	03/03/2004	Duane A. Burnett	CV06038US01	4535

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
BERCH, MARK L	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/792,346	BURNETT ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *10 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,12-19, 21-24* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/30/04,4/22/04*, 1/21/05, 9/27/04, 6/30/04(6)
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 20, drawn to Compounds, compositions and use, G is other than sugar or oligopeptide, classified in class 540, subclass 200.

II. Claims 10-11 drawn to Compounds, compositions and use, G is sugar residue, classified in class 536, subclass 29.11.

III. Claims (none), drawn to Compounds, compositions and use, G is oligopeptide, classified in class 930, subclass 280.

Claims 1-9, 12-19, 21-24 link inventions I and II and III. These claims are examined to the extent that they read on the elected invention.

The inventions are distinct, each from the other because of the following reasons: Sugars and peptides are considered to be clearly structurally very dissimilar to the other more ordinary organic groups recited.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ann Cannoni on 1/24006 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-9(part), 12-19(part), 20, 21-24(part). Affirmation of this election must be made by applicant in replying to this Office action. Claims 10-11, 27-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-9, 12-19, 21-24 are rejected as being drawn to an improper Markush Group. The claims are drawn to multiple inventions for reasons set forth in the above requirement for restriction. This does not constitute an art recognized genus. The claims are examined only to the extent that they read on the elected invention. Cancellation of the non-elected subject matter will overcome the rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 12-19, 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. A C_0 alkylene is impossible. An alkylene group must have at least one carbon.

2. It is unclear how applicants intend terms such as alkyl and alkenyl, etc. Alkyl is a group of the formula $-C_nH_{2n+1}$. But the page 18 description indicates that applicants actually intended the term to also cover substituted alkyl. If that is the case, the actual claim wording must reflect it. If applicants do not so intended, they can either amend the specification, or put the word "unsubstituted" in front of alkyl and other terms where this arises.
3. The use of $-N-N=N^-$ in Q4 is not correct, as it leaves one N atom without sufficient bonds, and a minus charge. Assuming that azido is intended, suggested is the conventional $-N_3$. Alternatively, applicants need to put in the second double bond plus internal charges.
4. The term "Diabetes" (claims 21, 23) is ambiguous. It is not a complete term. Diabetes insipidus for example is caused by the inability of the kidneys to conserve water, which is caused by a lack of ADH (central diabetes insipidus) or by failure of the kidneys to respond to ADH (nephrogenic diabetes insipidus). Applicants must select some specific form(s) of diabetes (e.g. Type 2 diabetes mellitus, or Gestational diabetes mellitus; these are metabolic disorders) and they must use that term, and show that one of ordinary skill in the art would have been able to determine that whatever term(s) is/are selected was the one(s) intended.
5. The term Sterol does not have a single, fixed meaning. Some definitions require that there be a hydroxyl group in the 3-position of the A-ring, but others require that it be present somewhere, no necessarily there. Some require that the material be a natural product derived from plants or animals, some do not.

6. The term "stanol" does not have a single well accepted definition. Is it any saturated phytosterol? Or any saturated sterol period, and in either case, what definition of phytosterol or sterol is being used?

Claims 1-9, 12-19, 21-24 are rejected under 35 U.S.C. 112, paragraphs 1 and 2, as the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically:

The molecule when G is an trialkylammoniumalkyl choice has a plus charge but no minus charge. A molecule without electrical neutrality is impossible to prepare and hence lacks enablement in terms of how to make, as such a thing cannot be made (paragraph 1). Note MPEP §2172.01: "A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See also MPEP §2164.08(c). Such essential matter may include missing elements ...". Here, the missing counterion is the missing element. On the other hand, if it was not the intention of applicants to claim such a non-neutral molecule, then the claim fails to set forth what applicants intend as their invention (paragraph 2). That is, it is not accurate because it is missing something. As stated in *In re Zletz*, 13 USPQ2d 1320, 1322, "An essential purpose of patent examination is to fashion claims that are precise, clear, correct and unambiguous."

Applicants need to locate the description of the counterion in the specification, and include that in claim 1.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Treatment of such disorders in general cannot be deemed enabled.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the huge scope of the many primary variables, trillions of compounds are embraced

(b) Scope of the diseases covered. There are quite a range of disorders.

A. Cardiovascular disorders embraces a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including Verrucous, Atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy, peripartum cardiomyopathy,

hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types of arrhythmias and atrial fibrillation. It covers elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural defects such as atrial septal defect (ASD), aorticopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riolan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers certain peripheral vascular disorders, such as deep-vein thrombosis and

thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilicalis, and verminous mesenteric arteritis. There are different forms of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia. There is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass, posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma, acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart

disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others.

B. Peripheral vascular disorders includes Raynaud's disease, acrocyanosis, frost bite, acute arterial occlusion, phlebitis, phlebothrombosis, diabetic gangrene, causalgia, shock and pheochromocytoma; intermittent claudication, digital ulceration, peripheral occlusive vascular disease, diabetic retinopathy and various lower extremity problems.

C. Cerebrovascular disorder include Vascular dementia, sometimes called cerebrovascular dementia is a term which encompasses a range of diseases or disorders. It is caused when small arteries in the brain burst (cerebral hemorrhage), or arteries are blocked by plaque formation or clots (thrombosis or embolism), or there is insufficient blood flow to parts of the brain (ischemia). Stroke is the most common cause, but it can arise from auto-immune inflammatory diseases of the arteries such as Systemic Lupus Erythermotsis and Temporal Arteritis; sometimes the cause is completely unknown. Among the various types, multi-infarct dementia (MID) is probably the most common. Other forms include Binswanger's Disease and Arteriosclerotic Dementia. There are many other Cerebrovascular disorders.

D. Preventing demylenation would involve either preventing or treating demyelinating diseases, in two broad categories. Primary demyelination is a loss of myelin sheaths with relative preservation of the demyelinated axons, arising either from damage to the oligodendroglia from a direct attack on the myelin itself. Secondary demyelination, occurs following axonal degeneration. For example, Leukodystrophies are diseases of the white

matter resulting from an error in the myelin metabolism, giving impaired myelin formation. Each involves the deficiency of a different enzyme. Examples include Krabbe's disease, Adrenoleukodystrophy (which exists in 4 forms), adrenomyeloneuropathy, Alexander Disease, Canavan Disease, Metachromatic Leukodystrophy (which exists in three forms), Pelizaeus-Merzbacher Disease, Refsum Disease, and Zellweger Syndrome. No pharmaceutical treatment is available to any of the leukodystrophies. Acute Necrotizing Hemorrhagic Leukoencephalitis is believed to be mediated by autoimmune attack on CNS myelin, triggered by a viral infection. It is usually fatal, generally just within days on onset. Other examples include Multiple Sclerosis (MS), progressive multifocal leukoencephalopathy, and Acute Disseminated Encephalomyelitis. Some are inherited diseases, such as peroneal muscular atrophy, hypertrophic polyneuropathy and Refsum's diseases.

E. Regulating levels of ß-amyloid peptides. More than a dozen of these have been found so far.

F. Diabetes cover central diabetes insipidus, nephrogenic diabetes insipidus, Type I and Type 2 diabetes mellitus, and Gestational diabetes mellitus. Some forms of diabetes, such as Type I DM, are not considered preventable.

G. The claims also cover an assortment of other diseases, including Alzheimer's Disease, and treatment and prevention of obesity and stroke.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors

involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information on page 31 is in the form of mg, not mg/kg. Further it is completely generic, with the same dosage regardless of disorder involved.

(4) State of the Prior Art: The compounds are azetidinones with a a particular substitution pattern at several positions. So far as the examiner in aware, azetidinones have not been used for many many items on this list, such as any form of diabetes, for Alzheimer's Disease, for any of the Leukodystrophies or Multiple Sclerosis, for stroke, etc.

(5) Working Examples: There are none at all. No data of any kind is presented.

(6) Skill of those in the art: The skill level in the art of pharmacological treatment of cardiovascular disorders varies with the disorder. In some areas such as hypertension it is relatively high. But in the great majority of cases it is very low as the disorders cannot be treated with pharmaceuticals. There are a wide variety of causes. For example, just for the Vascular dementias, these can be caused when caused when small arteries in the brain burst (cerebral hemorrhage), or arteries are blocked by plaque formation or clots (thrombosis or embolism), or there is insufficient blood flow to parts of the brain (ischemia). Stroke is the most common cause, but it can arise from auto-immune inflammatory diseases of the arteries such as Systemic Lupus Erythermotsis and Temporal Arteritis; sometimes the cause is completely unknown. A huge assortment of inflammatory processes

can result in various forms of vasculitis. Genetic defects and developmental problems are responsible for many types of structural problems. Metabolic disorders such as Mucopolysaccharidosis I (the cause of Hurler- Scheie syndrome) can cause vascular deposits of mucopolysaccharides with arteriosclerosis, heart murmur, and aortic regurgitation. The vast majority are treated either by surgical means or cannot be treated at all, leaving only general management of symptoms. The skill level for Alzheimer's Disease is considered low. Alzheimer's Disease is an extraordinarily difficult disease to treat, and has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon®, and Reminyl®), or voltage-dependent NMDA-antagonists (Memantine), properties these compounds are not disclosed to have.

(7) The quantity of experimentation needed: Owing especially to factors (1), (5) and (6), the quantity of experimentation is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claim Objections

Claim 20 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

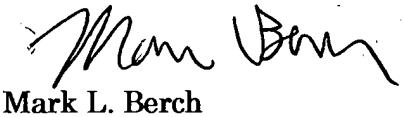
Specification

The abstract is objected to as vague. It gives too little of a description of the invented material.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Mark L. Berch
Primary Examiner
Art Unit 1624

3/29/2006